Chapter 8:

Inhaled corticosteroids do not affect behaviour

Tjalling W. de Vries, Eric N. van Roon,

Eric J. Duiverman.

Acta Paediatr 2008;97:786-789

Abstract

Introduction

Recently, we found that the most reports on suspected adverse effects of inhaled corticosteroids (ICS) dealt with behavioral problems. Therefore, we studied whether children with asthma and on ICS have more behavioral problems, such as aggressiveness and hyperactivity, as compared with healthy controls and children, under medical care because of other disorders.

Methods

Questionnaires were given to three groups of children: a group of asthmatic children with ICS a group of children attending the ENT outpatient clinic and healthy controls. Included were questions about health, medication use, demographical data and about behavior, including the Child Behavior Check List (CBCL) and questions about Attention Deficit Hyperactivity Disorders (ADHD).

Results

Forty asthmatic children on ICS, 50 children visiting the ENT outpatient clinic and 183 healthy controls were studied. The total CBCL and mean ADHD scores of the children on ICS were 28.1 and 9.1, which were both significantly higher than the scores of the healthy controls (20.4 and 7.1), but not when compared with the ENT outpatient group (26.2 and 8.6). Further analysis revealed statistically significant differences between the ICS group and healthy controls in CBCL-axes. There were, however, no differences between the ENT-group and the ICS on one side and the healthy controls on the other.

Conclusions

There is a difference in behavior between healthy children and asthmatic children on ICS, but not when compared with children, visiting the ENT department. Although hyperactivity, aggressiveness and anxiety might occur in children on ICS, this is probably caused by individual susceptibility. Being under specialist care can possibly explain behavioral differences between children on ICS and healthy controls.

Introduction

Inhaled corticosteroids (ICS) are effective drugs used preventively in childhood asthma and therefore their use is widely advised.[1,2,3] Well known side-effects in children are growth retardation, hoarseness, oral candidiasis, and adrenal suppression.[4] Recently, we described the reports of suspected adverse drug reactions of ICS, reported to the Netherlands Pharmacovigilance Centre Lareb.[5] A remarkable finding was that about 20% of the reports concerned effects on behaviour, such as hyperactivity and aggression. Behavioural problems in children who use ICS had been reported before.[6] It is not known whether this effect is a group effect or is a result of individual susceptibility. This prompted us to investigate whether a group of asthmatic children on ICS had more behavioural problems, such as hyperactivity and aggression, compared with healthy controls or children under the care of an otolaryngologist. We chose this group as a control group, because we hypothesised that sleep disorders, which can lead to behavioural problems, can occur in both asthma and otolaryngeal diseases. Paediatric controls were not included because about 11% of the children attending our outpatient hospital have psychological problems, such as Attention Deficit Hyperactivity Disorder (ADHD).[7]

Methods

Three groups of children were studied. The study group (ICS) were children aged 1 – 7 years, attending the outpatient clinic of our hospital, a large teaching hospital in the northern part of the Netherlands, in these children the diagnosis of asthma was made by paediatricians. The first control group (ENT) consisted of children of the same age, who attended the outpatient clinic of the Ear, Nose and Throat department of the same hospital. Children, who were under the care of other specialists or those with multiple medical problems, including psychological problems and ADHD, were excluded. In both groups, consecutive children visiting the outpatient clinic were invited. The parents were given the questionnaires by the secretarial staff before visiting the physician.

The second control group consisted of children of the same age, attending kindergarten and the first grades of primary schools in the city of Leeuwarden, and are referred to as CC (city controls). School and kindergarten personnel distributed the questionnaires. In an accompanying letter it was explained that we were looking for the influence of health, disease and treatment on the well-being of children.

The questionnaire contained questions about age and sex, social class, health, and whether the child was under the care of a physician. Also use of medication was asked for, as was the indication and the dose prescribed. When the latter was not given in the questionnaire of the ICS group, this was

searched for in the hospital computer system. The socio-economic status (SES) was estimated on the base of the highest professional level in the family. For this analysis the SES was divided in four categories: 1 not working; 2 routine/manual; 3 intermediate; 4 managerial/professional, as described elsewhere.[8]

The questionnaire contained two groups of statements about behaviour. The first set of statements was based on the DSM IV criteria for attention deficit hyperactivity disorder in three axes: attention deficit, hyperactivity, and impulsiveness.[9] Examples of the statements are: 'my child has difficulty keeping his attention focussed' and 'my child can not play quietly'.

The second set of statements was the Child Behaviour Check List (CBCL) for children of 18 – 60 months. The CBCL is designed and validated to identify behavioural problems in children.[10] The questionnaire we used is designed for children in the age group of 1 ½ - 5 years and we used it despite the fact that some children in this study were older, because the lists were used for comparison and not for individually diagnostic reasons. Examples of statements are: 'my child is disobedient', 'my child is cruel to animals', and my child eats too much.

The questions of the CBCL are grouped into five DSM-oriented problem-axes: affective, anxiety, pervasive development, attention deficit/hyperactivity, and oppositional defiant and eight empirically based axes: emotionally reactive, anxious/depressed, somatic complaints, withdrawn, sleep problems, attention problems, aggressive behaviour, and other problems.

Possible answers were 0, meaning absent; 1, meaning sometimes applicable; and 2, meaning that the specific trait applied very well to the child.

These numbers were summed and by doing so for every child a result on every axis was computed. Means and standard deviations for all axes were computed for the three groups. For every axis a normal range is defined and we computed for every child whether the outcome for that child was within the normal range or not. Then the proportions of children within and outside the normal range between the groups were compared.

We used the Wilcoxon test for ordinal data and the chi square test for binominal results, and performed linear and logistic regression analysis. A p-value < 0.05 was considered statistically significant. Data were analysed using SPSS for Windows (version 11.0). The regional ethical committee approved this study.

Results

In January 2006 320 questionnaires were distributed in the kindergartens and schools, 269 were received back. Of these 23 were excluded because of insufficient answers and another 63 were excluded because it was reported that these children were under the care of a physician and therefore were considered not healthy. The remaining questionnaires of 183 healthy children were included. The lists for the ICS and ENT were distributed in the period of March to June 2006. In the ICS group data of 40 children were included and in the ENT group data of 50 children.

Table 1 compares the groups for age, sex, and social class. The median age for the children in the ICS group is 53 months (range 22 – 82) and of the controls is 58 months (24 – 84). The children of the ENT group are significantly younger (42 months; range 18 – 84) than the ICS and CC children. The proportion of boys in the ICS group is significantly higher than in both control groups. The distribution of the social classes in both groups is comparable. Of the children under the otolaryngology's care 10 had adenotonsillar hypertrophy (20%), 13 had recurrent otitis (26%); the complaints of the remaining 27 children (54%) were not specified.

Table 1: baseline characteristics of the groups.

	ICS 40	CC 183	ENT 50
Gender			
Male (%)	73*	49	42
Age (months)			
Median (range)	53 (22 – 82)	60 (24 – 84)	42 (18 – 84)**
Social class (%)			
1 not working	0	1	2
2 routine/manual	51	41	54
3 intermediate	41	44	25
4 managerial/professional	8	14	19

** there are statistically significantly more boys in the ICS group; between ICS and CC p = 0.01 and between ICS and ENT p = 0.00.*
*** the children of the ENT group were statistically significantly younger than the children in the ICS and City control group. Between ICS and ENT p = 0.03, between CC and ENT p = 0.00.*

It appeared that all children on ICS used fluticasone. The mean median daily dose was 250 µg (range 50 – 500 µg). Of these 40 children 16 used the combination of fluticasone and salmeterol.

The mean score of the ADHD symptoms in the ICS group is 9.1 and in the healthy control group 7.1, this difference is statistically significant (table 2 and 3). Analysis of the subsets of questions revealed that hyperactivity symptoms are reported significantly more often in the ICS group. However, there

were no significant differences between the ENT and ICS groups, and there were no significant differences between the ENT and CC groups. In children on a higher dose of ICS behavioural problems were not more reported. The mean score of the CBCL questionnaire in the ICS group is 28.1 and of the healthy controls it is 20.4. This difference is statistically significant. In the subsets of questions there are statistically significant differences for the sets of affective disorders, anxiety, depression, somatic complaints, and 'other problems'. There were no significant differences between the ENT and ICS groups and also not between the ENT and CC groups. There were significantly more children with affective problems and somatic complaints in the ICS group, compared with the City controls. However, comparison between the ICS and ENT groups on one hand, an ENT and City control groups on the other, revealed no statistically significant differences. Linear and logistic regression analysis revealed that sex, age, and SES did not influence the outcomes.

Table 2. Comparison for results of the scores of ADHD and CBCL questionnaires between children on ICS (ICS), healthy controls (CC) and children attending the ENT-outpatient clinic (ENT). Median values are given.

Item	ICS	CC	ENT
Number of children	40	183	50
ADHD			
Attention deficit	4.5	3.0	4.0
Hyperactivity	3.0*	2.0	2.0
Impulsiveness	1.0	1.0	1.0
Total ADHD	9.5*	6.0	8.5
CBCL			
DSM-oriented problem-axes			
Affective	2.0*	1.0	1.0
Anxiety	2.0*	1.0	2.0
Pervasive development	2.0	2.0	2.0
Attention deficit/hyperactivity	3.0	2.0	2.5
Oppositional/defiant	3.0	3.0	3.0
empirically based axes			
Emotionally reactive	1.5	1.0	1.0
Anxious/depressed	2.0*	1.0	1.0
Somatic complaints	1.0*	1.0	1.0
Withdrawn	1.0	1.0	1.0
Sleep problems	1.0	1.0	1.0
Attention problems	1.0	1.0	1.0
Aggressive behaviour	7.0	6.0	7.0
Other problems	7.0*	4.0	5.0
Total CBLC	23.0*	20.0	22.5

** denotes that these score are statistically significant higher for children on ICS (ICS) compared with healthy controls (CC). The p-values were 0.02 for hyperactivity and 0.03 for the total score of ADHD-symptoms, 0.01for affective; 0.02 for anxiety; 0.02 for anxious/depressed; 0.01 for somatic complaints; 0.02 for other problems and 0.04 for the total score of the CBCL. There were no statistically significant differences when healthy children and ENT-children are compared, nor when ENT-children and children on ICS were compared.*

Table 3: Comparison for results of the scores of ADHD and CBCL questionnaires between children on ICS (ICS), healthy controls (CC) and children attending the ENT-outpatient clinic (ENT). Means and standard deviations (s.d) are given. Value above the cut off level are considered abnormal. For the scores of other problems' and 'total CBCL' no cut off levels exist.

Item Number of children	ICS 40	CC 183	ENT 50	cut off level
ADHD				
Attention deficit	4.7 (3.3)	3.7 (3.2)	4.6 (3.5)	10
Hyperactivity	3.4 (2.5)*	2.4 (2.5)	3.1 (3.0)	6
Impulsiveness	1.0 (1.0)	0.9 (0.9)	0.9 (0.9)	2
Total ADHD	9.1 (5.7)*	7.1 (5.6)	8.6 (6.4)	22
CBCL				
DSM-oriented problem-axes				
Affective	2.3 (2.4)*	1.3 (1.5)	1.9 (2.3)	6
Anxiety	3.0 (3.1)*	1.7 (2.0)	2.4 (3.2)	8
Pervasive development	2.7 (3.0)	2.3 (2.6)	2.6 (3.1)	8
Attention deficit/hyperactivity	3.1 (2.5)	2.7 (2.2)	3.4 (2.8)	10
Oppositional/defiant	3.3 (2.7)	2.9 (2.4)	3.3 (2.6)	8
empirically based axes				
Emotionally reactive	2.2 (2.5)	1.8 (2.1)	2.2 (2.5)	8
Anxious/depressed	2.3(2.4)*	1.5 (1.8)	1.9 (2.7)	8
Somatic complaints	2.2 (3.1)*	1.1 (1.6)	1.3 (1.8)	6
Withdrawn	1.1 (1.5)	1.0 (1.3)	1.3 (2.0)	5
Sleep problems	2.0 (2.6)	1.4 (1.8)	1.7 (2.6)	8
Attention problems	1.8 (1.8)	1.4 (1.5)	1.9 (1.8)	6
Aggressive behaviour	8.1 (6.5)	6.5 (5.4)	8.0 (6.2)	24
Other problems	7.5 (6.7)*	5.0 (4.5)	6.8 (6.0)	
Total CBLC	28.1(22.1)*	20.4 (16.1)	26.2 (21.6)	

** denotes that these score are statistically significant higher for children on ICS (ICS) compared with healthy controls (CC). The p-values were 0.02 for hyperactivity and 0.03 for the total score of ADHD-symptoms, 0.01for affective; 0.02 for anxiety; 0.02 for anxious/depressed; 0.01 for somatic complaints; 0.02 for other problems and 0.04 for the total score of the CBCL.*
There were no statistically significant differences when healthy children and ENT-children are compared, nor when ENT-children and children on ICS were compared.

Discussion

We found that parents reported that there are more behavioural problems in young children with asthma symptoms and using ICS, compared with healthy children. Hyperactivity was reported more often in this group but aggressiveness was not. However, in comparison with children attending the ENT outpatient clinic there are no significant differences for any of the axes studied. This could mean that the behavioural problems in children with asthma and on ICS are simply due to the fact that they are under specialist care.

Systemic steroids can influence the behaviour of patients. In a recent review Stuart et al discuss the

influence of systemic steroids on behaviour.[11] Steroid psychosis occurs in 5% of adults on systemic steroids, and there are also several case reports of steroid psychosis in children. Adverse psychological effects of steroids in children include anxiety, aggressiveness, depressive symptoms, euphoria, and hyperactivity.[11]

Clinical trials on systemic corticosteroids and behaviour are rare. To our knowledge, Kayani et al were the only ones who studied the influence of oral steroids in acute asthma exacerbations. They found statistically significantly more anxiety and aggressive behaviour in children using 2 mg/kg, compared to 1 mg/kg.[12]

Psychic adverse effects of ICS have been described before. Hederos described a group of 60 children of whom 9 (15%) experienced more hyperactivity and aggressiveness after relatively high doses of budesonide (770 µg daily).[6] In the review of Stuart 8 children with adverse psychic effects such as hyperactivity and insomnia were described.[11] In our study on the suspected adverse drugs reports in the Netherlands, 19% of all reports were on negative effects on behaviour, including hyperactivity and anxiety.[5] On the other hand, Bender compared the effect on behaviour in children on inhaled beclomethasone versus children who used theophylline and found no effects, nor differences between the two groups.[13] There may be several possible explanations; first the tests were not sensitive enough to detect subtle behavioural problems, second a lack of statistical power, and third behavioural abnormalities may exist after use of ICS as well as after theophylline therapy.

There are a few publications on the relationship between behavioural problems and asthma or recurrent wheeze. In a large meta-analysis regarding studies on behaviour and asthma including results of nearly 5000 children, it was concluded that children with asthma had more behavioural problems than healthy controls.[14] The most frequently mentioned problems were anxiety and depression. Hyperactivity and aggression were less linked to asthma. However, the use of medication was not mentioned and there were no comparisons with children with other forms of medical care.[14]

More recently, Haltermann et al studied behaviour in inner-city children. They found that there were more behavioural problems, such as anxiety, in children with asthma compared to healthy controls. However, the use of medication was not mentioned, and in this study no control group of children with other chronic diseases was included.[15]

In an interesting study, Calam et al found that behavioural problems precede the development of wheeze in childhood. They gave questionnaires on the child's behaviour at the age of three and studied the children at the age of 5 years. In the group of late onset wheezers the incidence of behavioural problems was significantly higher than in children who never wheezed.[8] However, no specification

of the behavioural problems or explanation for this phenomenon was given here. They also did not compare this group with children with other medical problems.

In other groups of children with chronic diseases, such as diabetes,[16] and constipation,[17] an increase of behavioural problems, compared with healthy controls, has been described. Therefore, it could be possible that the behavioural differences between healthy children and children with asthma is not a result of the asthma or of the medication used, but merely an indication that having a condition for which medical care is sought influences the child's behaviour or the assessment of it by the parents. We choose to compare children with asthma and ICS with children who visited the ENT department because we hypothesised that in both groups sleep disturbances can occur and sleep problems may influence daytime behaviour. The latter has been confirmed by Goldstein et al, who studied children before and after tonsillectomy and found a correlation between sleep apnoea and behaviour.[18] In this study there were no differences in sleep problems between the groups.

An important limitation of this study is that we did not study the children formally by an independent professional and relied on the parents' interpretation of the child behaviour and did not do this study in a double blind fashion. However, by comparing the groups interpretations might be the same in all groups.

The most reliable method of studying the behaviour in children would be to expose children with asthma in a randomised controlled trial to ICS and placebo. However, it would be difficult and unethical, to do such a study.

Another limitation could be that the groups are too small. However, we found a statistically significant difference between two groups but this difference evaporated when a second control group was also studied. We recognize that there were more boys in the group on ICS and that the age of the children visiting the ENT department was younger, but we could not demonstrate a significant influence on the results.

We conclude that behavioural problems as reported in the children investigated here are not frequent. Hyperactivity or aggressiveness occurs only in a few, probably more susceptible children. The behavioural problems seen in children with ICS could be due to the fact that they have a chronic condition, which affects normal life. Conclusions about behavioural influences of asthma and medication have to be drawn very carefully. In studies on behavioural effects of diseases or treatments not only healthy controls should be included, but also children with other diseases.

We thank the parents of the children who returned the questionnaires for their cooperation and the personnel of the outpatient clinics who asked parents to participate. Also we thank the personnel and managements of the schools and kindergartens for their help. Aseba is acknowledged for the kind permission to use the modified questionnaire. Dr. J. Collins reviewed the English.

References

1 Global Initiative for Asthma (GINA). Pocket guide for asthma management and prevention in children. December 2006.
2 Anonymous. British guidelines on the management of asthma: Pharmacological management. Thorax 2003;58(suppl 1): s17-s31.
3 Duiverman EJ, Brackel HJL, Merkus PJFM, Rottier BL, Brand PLP. Richtlijn 'astmabehandeling bij kinderen' van kinderlongartsen.(2e herziening). II Medicamenteuze behandeling. Ned Tijdschr Geneeskd 2003;147: 1909-1912.
4 Lipworth BJ. Systemic adverse effects of inhaled corticosteroid therapy: A systematic review and meta-analysis. Arch Intern Med 1999;159: 941-955.
5 Vries de TW, Langen –Wouterse de JJ, Puijenbroek van EP, Duiverman EJ, Jong – Van den Berg de LTW. Reported adverse drug reactions during the use of inhaled steroids in children with asthma in the Netherlands. Eur J Clin Pharm 2006;62:343-346.
6 Hederos C. Neuropsychologic changes and inhaled steroids. J Allergy Clin Immunol 2004;114: 451-452.
7 De Vries TW, Wierdsma N, Van Ede J, Heijmans HSA. Dieting in children referred to the pediatric outpatient clinic. Eur J Ped 2001;160:595-8
8 Calam R Gregg L, Simpson A, Simpson B, Woodcock A, Custovic A. Behavior problems antecede the development of wheeze in childhood. Am J Respir Crit Care Med 2005;171:323-327.
9 American Psychiatric Association. Diagnostic and statistical manual of mental disorders. IV-TR 4th edition. Washington 2005.
10 Achenbach TM. Integrative guide for the 1991 CBCL/4-18, YSR and TRF profiles. Burlington VT: University of Vermont Department of Psychiatry, 1991.
11 Stuart FA, Segal TY, Keady S. Adverse psychological effects of corticosteroids in children and adolescents. Arch Dis Child 2005;90:500-506.
12 Kayani S, Shannon DC. Adverse behavioural effects of treatment for acute exacerbation of asthma in children. Chest 2002;122:624-628.
13 Bender BC, Ikle DN, DuHamel T, Tinkelman D (1998) Neuropsychological and behavioral changes in asthmatic children treated with beclomethasone dipropionate versus theophylline. Pediatrics 101: 355-360.
14 McQuaid EL, Kopel SJ, Nassau JH. Behavioral adjustment in children with asthma: a meta-analysis. J Dev Behav Pediatr 2001;22:430-39.
15 Halterman JS, Conn KM, Forbes-Jones E, Fagnano M, Hightower AD, Szilagyi PG. Behavior problems among inner-city children with asthma: findings from a community-based sample. Pediatrics 2005; 117:e192-e199.
16 Holmes CS, Respess D, Greer T, Frentz J. Behavior problems in children with diabetes: disentangling possible scoring confound on the child behaviour checklist. J Ped Sociol 1998;23:179-185.
17 Benninga MA, Voskuijl WP, Akkerhuis GW, Taminiau JA, Bueller HA. Colonic transit times and behaviour profiles in children with defecation disorders. Arch Dis Child 2004;89:13-16.
18 Goldstein NA, Fatima M, Campbell TF, Rosenfeld RM. Child behaviour and quality of life before and after tonsillectomy and adenoidectomy. Arch Otolaryngol Head Neck Surg 2002;128:770-775.